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Two Methyl, Two *t*-Butyl or Two Allyl Substituents on Chiral Positions
Next to the Pyridine Ring

by

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Abstract

Chiral 2,16-diallyl-, 2,16-dimethyl- and 2,16-di-*t*-butylpyridino-18-crown-6 ligands have been prepared by treating the appropriate chiral α,α'-disubstituted pyridinedimethanol with tetraethyleneglycol ditosylate in the presence of base. In these reactions, chiral 2:2 dimers (dipyridino-36-crown-12 derivatives) were also obtained.

Introduction

Since the pioneering work of Cram and his co-workers on chiral crown ethers based on the "naphthalene wall", [1] enantiomeric recognition of optically active amino acids and organic ammonium ions by chiral crowns and their analogues has received much attention. [2] In order to develop qualitative and quantitative relationships between molecular structural features of chiral crown ether hosts and chiral organic ammonium ion guests, we have prepared a series of chiral crown ethers, azacrown ethers and crown ether-diesters having pyridine, triazole and pyrimidine subcyclic units. [3-14] Thermodynamic and kinetic parameters for chiral host - chiral guest interactions have been determined using ^{1}H NMR spectroscopy, titration calorimetry and Fourier transform ion cyclotron resonance mass spectrometry techniques. [4, 7, 8, 10-12, 14, 15-18] To expand our research on the chiral host - chiral guest interactions by the pyridino-crown ethers, we have prepared new pyridino-18-crown-6 ligands containing substituents on chiral positions next to the pyridine ring (in positions 2 and 16). Computer and CPK modeling shows that introduction of allyl or alkyl groups at the 2- and 16-positions in pyridino-18-crown-6 gives an effective chiral barrier in the crown ring and increases the rigidity around the chiral barrier. [19] The rigidity may prevent a "splaying motion" [20] in the molecule which would greatly reduce enantiomeric recognition. Therefore, it is expected that the 2,16-disubstituted pyridino-18-crown-6 derivatives would exhibit high enantiomeric recognition for chiral organic ammonium ions. Li et al. reported that chiral 2,16-dimethyl-substituted triazolo-18-crown-6 having cholesteryl or *n*-dodecyl groups as lipophilic side arms exhibited high chiral recognition for the enantiomers of several organic ammonium ions. [21] Those results also support our supposition.

This report describes the synthesis of meso and chiral 2,16-diallyl-, 2,16-dimethyl- and 2,16-di-*t*-butyl-substituted pyridino-18-crown-6 ligands. In these preparation, we also isolated meso and chiral 2:2 dimers (the dipyridino-36-crown-12) for the first time.

Results and Discussion

Synthesis and Structure. α,α'-Diallylpyridinedimethanol (meso-, (-)- and (+)-1) were prepared by the Grignard reaction of 2,6-pyridinedicarboxaldehyde and allylmagnesium chloride (Scheme 1). Resolution of (-)-1 and (+)-1 from the racemic mixture was carried out using a Regis-Pirkle HPLC column to give optically pure (-)-1 (92.8 % ee, 46 % yield) and (+)-1 (99 % ee, 17 % yield). The structures of meso-1, (-)-1 and (+)-1 were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. Chiral α,α'- dimethyl- and di-t-butylpyridinedimethanols (meso-2, (S,S)-(-)-2 [22] and (S,S)-(-)-3 [23]) were prepared and resolved according to the procedures described in the literature. [22,24]

Using these chiral α,α'-disubstituted pyridinedimethanols, new chiral macrocycles were prepared as shown in Scheme 2. The reactions of diallyl- and dimethyl-substituted pyridinedimethanols with tetraethyleneglycol ditosylate in the presence of base gave not only pyridino-18-crown-6 derivatives (4a and 5a) but also the 2:2 dimers (dipyridino-36-crown-12 derivatives 4b and 5b). However, when di-t-butylpyridinedimethanol (S,S)-(-)-3 was used, only monomer (S,S)-(-)-6a was isolated.

The structures of meso-, (-)- and (+)- 4a and 5a were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analyses (the elemental composition of (S,S)-(-)-6a was confirmed by elemental analysis instead of HRMS). We could not use the HRMS data for molecular analyses of 2:2 dimers 4b and 5b because the parent ion peak could not be observed in the FAB mass spectra. However, the structures of 4b and 5b were confirmed by detailed analysis of the ^{1}H NMR, ^{13}C NMR, EI and FAB mass spectral data. In all cases, meso-, (-)- and (+)- derivatives showed the same ^{1}H and ^{13}C NMR spectra in CDCl$_3$. When the ^{1}H NMR spectra of meso-4a and the chiral-forms of 4a were measured in benzene-d$_6$, there were no chemical shift changes in the allyl protons, although a small change for the methylene protons of the crown ring was observed. On the other hand, the spectra of the 1:1 and 2:2 macrocycles exhibited significant differences. The differences in ^{1}H

NMR spectra of **4a** and **4b** (Figure 1) are as follows: (i) a doublet at $\delta = 7.34$ for the protons at the 3-position in the pyridine ring of **4a** appear at a higher field ($\delta = 7.18$) in the spectrum of **4b**, (ii) a multiplet for the -CH_2CH_2O- units in **4b** is more simple than that of **4a**, and (iii) although the signal for the allyl protons at $\delta = 2.57$ for **4a** splits into a triplet, that of **4b** splits into an octet. Figure 2 shows the calculated splitting patterns of the allyl moieties of **4a** and **4b**, which are presumed to have $A_2(B)MXY$ and $AA'(B)MXY$ patterns, respectively. If the above assumptions are correct, when the H_B proton is decoupled, signals for the allyl protons at $\delta = 2.57$ (H_A and $H_{A'}$) in **4a** and **4b** should be changed to a doublet and a heptet, respectively. Figure 3 shows the spectral change in the allyl proton splitting before and after irradiation to the H_B protons. As we expected, when irradiated, a doublet in **4a** and a heptet in **4b** were observed. Computer modeling indicates that the macroring is twisted and, therefore, the allyl substituents in **4b** are in a more crowded space than those in **4a**. Thus, the more complicated splitting pattern in 2:2 dimer **4b** is due to a slow rotation rate of the allyl moiety in the NMR time scale.

The ^{13}C NMR spectra reflect the carbon skeletons of molecules. In the ^{13}C NMR spectra of **4a** and **4b**, the chemical shift of the corresponding carbons in each structure appears at almost the same positions (see experimental section). The exceptions are as follows: (i) signals for carbons at position 3 on the pyridine ring in **4b** (120.8 ppm) appear at a lower field by 1 ppm than those of **4a** (119.8 ppm), and (ii) although there are four signals for the -CH_2CH_2O- carbons at 71.2, 70.8, 70.7 and 69.1 ppm in **4a**, only three signals at 70.8 (intense signal), 70.7, and 68.6 ppm appear in **4b**. The more flexible ethyleneoxy units of the dimer (**4b**) should provide a more simplified ^{13}C NMR spectral pattern. Thus, the ^{13}NMR spectrum of **4b** indicates that it is the 2:2 dimer.

As described above, parent ion peaks in the FAB mass spectra could not be observed for the 2:2 dimers. However, we could assign the fragment ion peaks. In the EI mass spectra for **4b**, fragment ion peaks at 754 (observed only meso-**4b**), 377 and 336 are assigned for $[M]^+$, $[M/2]^+$ and

$[M/2-CH_2CH=CH_2]^+$, respectively. Although a parent ion peak arising from M^+ is usually observed in a FAB mass spectrum, only fragment ion peaks could be observed for **4b**. The fragment ion peaks at 706 ($683+Na^+$), 684 ($683+1$), 616 ($593+Na^+$), 594 ($593+1$), 400 ($377+Na^+$) and 378 ($377+1$) could be reasonably assigned to the species shown in Figure 4. In all FAB mass spectra of meso-, (-) and (+)-**4b**, the fragment ion at 594 ($593+1$ in Figure 4) is the base peak. This observation suggests that the fragment ion at 594 is formed directly from **4b** or from the fragment ion at 684 ($683+1$ in Figure 4). These EI and FAB mass spectral data strongly suggest that **4b** is the 2:2 dimer. The mass spectral experiments also suggest that the 2:2 dimer is readily cleaved under EI and FAB mass spectral conditions. The structures of the other 2:2 dimers were confirmed in the same manner.

Experimental

Materials and Apparatus.   Meso-, (-)- and (+)- 2,6-di-*t*-butyl- and 2,6-dimethyl-substituted-pyridinedimethanol were prepared as reported.[22, 24] The ^{1}H and ^{13}C NMR spectra were obtained at 200 MHz. The ^{1}H NMR spectra for calculation of log K values were obtained at 500 MHz.

Synthesis and Resolution of α,α'-Diallyl-2,6-pyridinedimethanol (meso-1, (-)-1 and (+)-1).   A solution of 2,6-pyridinedicarboxaldehyde (2.83 g, 20.9 mmol) in dry THF (75 mL) was added dropwise over a period of 30 min to a 2.0 M solution of allylmagnesium chloride in THF (22 mL, 44.0 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was then quenched by the addition of 50 mL of water. The organic and aqueous layers were separated, and the aqueous layer was extracted with ether (75 mL x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was eluted from a silica gel column with 4/1: hexane/ethyl acetate to give 1.11 g (24 %) of the (±)-diol (mixture of (-)-**1** and (+)-**1**) and 0.90 g (20 %) of the meso-diol (meso-**1**). Meso-**1** was an oily white solid; ^{1}H NMR (CDCl$_3$): δ 7.70 (t, J = 7.7 Hz, 1H), 7.23 (d, J = 7.7 Hz, 2H),

3.61 (broad s, 2H), the allyl moiety showed an AA'(B)MXY pattern; δH_A: 2.66 (quin, 2H), $\delta H_{A'}$:

2.49 (quin, 2H), δ_B: 4.83 (dd, 2H), δH_M: 5.82 (m, 2H), δH_X: 5.12 (q, 2H), δH_Y: 5.11 (q, 2H),

$J_{AA}(gem)$ = 13.7 Hz, J_{AM} = J_{AB} = 6.0 Hz, $J_{MX}(trans)$ = 15.5 Hz, $J_{MY}(cis)$ = 11.9 Hz; ^{13}C NMR

(CDCl$_3$): δ 162.6, 137.6, 134.2, 119.3, 118.5, 72.6, 43.0; HRMS; Calcd for $C_{13}H_{17}NO_2$: 219.1259.

Found: 219.1241.

A mixture of the (±)-diol (1.10 g, 5.02 mmol), 4-dimethylaminopyridine (0.219 g, 5.02

mmol), triethylamine (200 mL), and acetic anhydride (100 mL) was stirred at rt under Ar for 1.5

h. The mixture was then concentrated under reduced pressure and eluted from a silica gel

column with hexane/ethylacetate: 4/1 to give 1.35 g of the racemic diacetate. The diacetate was

dissolved in 13.5 mL of 25 % CHCl$_3$ and 1 % i-C$_3$H$_7$OH and injected onto a Regis-Pirkle Type

1-A Semi Preparative Chiral HPLC (25 cm x d. 10 mm) column. Repeated injections of 20 μL

each and elution with 1 % i-C$_3$H$_7$OH in hexane (flow rate 3 mL/min) gave 0.280 g of the first

eluted enantiomer (retention time = 20.6 min) and 0.490 g of the second eluted enantiomer

(retention time = 21.5 min). The enantiomers were stirred in K$_2$CO$_3$ saturated CH$_3$OH (140 mL

for the first enantiomer and 225 mL for the second) for 1 h, and the CH$_3$OH was removed under

reduced pressure. The residue was dissolved in H$_2$O (40 mL for the first enantiomer and 50 mL

for the second) and extracted with ether (75 mL x 4 for the first enantiomer and 100 mL x 4 for

the second enantiomer). The dried (MgSO$_4$) ether extracts were concentrated under reduced

pressure to give 0.175 g of diol (+)-1 (99 % ee by HPLC) derived from the first eluted enantiomer

and 0.354 g of diol (-)-1 (92.8 % ee by HPLC) derived from the second eluted enantiomer. This

represents a 16 % yield of the (+)-1, a 32 % yield of the (-)-1, and a 48 % yield for the entire

resolution process. (+)-1 solidified on standing in the refrigerator, mp. 49 - 51 °C; $[\alpha]^D_{25}$ = +102°

(c = 0.85, C$_2$H$_5$OH); HRMS; Calcd for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1240. (-)-1 solidified

on standing in the refrigerator, mp. 48 - 50 °C; $[\alpha]^D_{25}$ = -81.1° (c = 0.90, C$_2$H$_5$OH); HRMS; Calcd

for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1239. The ^1H and ^{13}C NMR spectral data for (-)-1 and

(+)-1 were the same as that of the meso-isomer reported above.

Preparation of meso-2,16-Diallyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4a) and meso-2,16,22,36-Tetraallyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (4b) (Scheme 2). Meso-diallyl-substituted pyridino-crown ethers were prepared using two procedures as follows:

(i) K (0.12 g, 3.05 mmol) was added to 25 mL of t-BuOH under Ar. The solution was heated to 70 °C for 40 min and then cooled to rt. Meso-α,α'-diallylpyridinedimethanol (meso-1) (0.20 g, 0.91 mmol) in t-BuOH (20 mL) was added dropwise and the mixture was stirred for 2 h at 70 °C. After the solution was cooled to rt, tetraethyleneglycol ditosylate (0.528 g, 1.05 mmol) in 20 mL of dry THF was added dropwise over the period of 20 min. The mixture was stirred for 6 days at rt and then at 100 °C for 1 h. After the reaction mixture was cooled, 25 mL of CH_2Cl_2 and 20 mL of distilled H_2O were added. The CH_2Cl_2 layer was separated and the H_2O layer was extracted with CH_2Cl_2 (20 mL x 2). The CH_2Cl_2 solutions were combined and evaporated under reduced pressure. The residual oil was chromatographed on alumina using 100/1: toluene/ethanol as eluent. The second fraction was further purified by gel-permeation (Sephadex LH-20 with C_2H_5OH as eluent) to give 0.022 g of meso-**4a** (6 %) and 0.020 g of the dimer meso-**4b** (6 %) as oils.

(ii) Meso-**1** (0.070 g, 0.32 mmol) in t-BuOH (10 mL) was added dropwise to 10 mL of t-BuOH containing K (0.039 g, 1.0 mmol) under Ar. After the solution was stirred for 16 h at rt, tetraethyleneglycol ditosylate (0.194 g, 0.39 mmol) in 7 mL of dry THF was added dropwise over a period of 15 min. The mixture was stirred for 6 days at rt. Although the spot for the ditosylate disappeared in alumina TLC, the spot for the diol did not. K (0.033 g, 0.85 mmol) and ditosylate (0.150 g, 0.30 mmol) were further added and stirring continued for 28 h at rt. The spot for the diol disappeared and, therefore, the reaction mixture was evaporated under reduced pressure at rt. The residual solid was dissolved in $C_6H_5CH_3$, and separated on an alumina column

($C_6H_5CH_3/C_2H_5OH$: 300/1). The second fraction was further purified by gel-permeation to give 0.039 g of meso-**4a** (33 %) as an oil. Under these reaction conditions, the dimer meso-**4b** could not be obtained. Meso-**4a** exhibited the following properties, ^1H NMR (CDCl$_3$): δ 7.70 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 2H), 4.60 (dd, $J = 7.1$ Hz, 2H, H$_B$), 3.83 -3.30 (m, 16H), the allyl moiety of meso-**4a** showed an A$_2$(B)MXY pattern, δH$_A$: 2.57 (dd, 4H), δH$_M$: 5.81 (m, 2H), δH$_X$: 5.04 (q, 2H), δH$_Y$: 5.01 (q, 2H), $J_{AM} = J_{AB} = 7.1$ Hz, $J_{MX}(trans) = 16.9$ Hz, $J_{MY}(cis) = 9.9$ Hz, $J_{XY}(gem) = 2.1$ Hz; ^{13}C NMR (CDCl$_3$): δ 161.2, 137.0, 134.7, 119.8, 117.3, 83.6, 71.2, 70.8, 70.7, 69.1, 41.0; HRMS; Calcd for $C_{21}H_{31}NO_5$: 378.2289. Found: 378.2280. Meso-**4b** (from (i)) exhibited the following properties, ^1H NMR (CDCl$_3$): δ 7.62 (t, $J = 7.7$ Hz, 2H), 7.18 (d, $J = 7.7$ Hz, 4H), 4.59 (dd, $J = 6.7$ Hz, 4H, H$_B$), 3.68 -3.38 (m, 32H), the allyl moiety of meso-**4b** showed an AA'(B)MXY pattern, δH$_A$: 2.68 (quin, 4H), δH$_{A'}$: 2.58 (quin, 4H), δH$_M$: 5.77 (m, 4H), δH$_X$: 5.01 (q, 4H), δH$_Y$: 4.98 (q, 4H), $J_{AA'}(gem) = 14.1$ Hz, $J_{AM} = J_{AB} = 6.7$ Hz, $J_{MX}(trans) = 17.1$ Hz, $J_{MY}(cis) = 10.2$ Hz, $J_{XY}(gem) = 1.5$ Hz; ^{13}C NMR (CDCl$_3$): δ 161.1, 136.4, 134.8, 120.8, 117.1, 82.8, 70.8, 70.7, 68.6, 40.7; EI-MS: 160 (100 %), 336 (22 %), 377 (M$^+$/2, 4 %), 754 (M$^+$, 0.5 %); FAB-MS: 378 (5 %), 400 (377+Na$^+$, 16 %), 486 (49 %), 508 (485+Na$^+$, 26 %), 594 (100 %), 616 (593+Na$^+$, 81 %), 684 (18 %), 706 (683+Na$^+$, 5 %). As the parent ion peak could not be observed by FAB-MS, the HRMS could not be measured.

Preparation of (-)-2,16-Diallyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4a) and (-)-2,16,22,36-Tetraallyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (4b) (Scheme 2). The reaction of (-)-diol **1** with tetaethyleneglycol ditosylate was carried out using method (ii) described above using 0.098 g of the (-)-diol **1** to give 0.025 g of (-)-**4a** (15 %) and 0.041 g of (-)-**4b** (24 %) as oils. (-)-**4a** gave the following properies, $[\alpha]^{25}_D = $ - 2.4 ° (c = 1.0, CHCl$_3$); HRMS; Calcd for $C_{21}H_{31}NO_5$: 378.2289. Found: 378.2283. (-)-**4b** gave the following properies, $[\alpha]^{25}_D = $ - 48 °(c = 0.55, CHCl$_3$); EI-MS: 160 (100 %), 336 (80 %), 377 (M$^+$/2, 20 %); FAB-MS: 378 (4 %), 400

(377+Na⁺, 7 %), 486 (54 %), 508 (485+Na⁺, 7 %), 594 (100 %), 616 (593+Na⁺, 24 %), 684 (25 %), 706 (683+Na⁺, 3 %). Because the parent ion peak could not be observed by FAB-MS, the HRMS could not be measured. The ^{1}H and ^{13}C NMR spectra of (-)-**4a** and (-)-**4b** were the same as those of the meso-compounds.

Preparation of (+)-2,16-Diallyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (4a) and (+)-2,16,22,36-Tetraallyl-3,6,9,12,15,23,26,29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (4b) (Scheme 2). The reaction of (+)-diol **1** with tetaethyleneglycol ditosylate was carried out using method (ii) described above using 0.078 g of (+)-diol **1** to give 0.020 g of (+)-**4a** (15 %) and 0.011 g of (+)-**4b** (8 %) as oils. (+)-**4a** exhibited the following properties, $[\alpha]^{25}_D = + 2.2$ ° (c = 1.0, CHCl$_3$); HRMS; Calcd for C$_{21}$H$_{31}$NO$_5$: 378.2289. Found: 378.2283. (+)-**4b** exhibited the following properties, $[\alpha]^{25}_D = + 44$ ° (c = 0.66, CHCl$_3$); EI-MS: 160 (100 %), 336 (59 %), 377 (M⁺/2, 11 %); FAB-MS: 378 (5 %), 400 (377+Na⁺, 16 %), 486 (41 %), 508 (485+Na⁺, 27 %), 594 (100 %), 616 (593+Na⁺, 52 %), 684 (10 %), 706 (683+Na⁺, 4 %). Because the parent ion peak could not be observed by FAB-MS, the HRMS could not be measured. The ^{1}H and ^{13}C NMR spectra of (+)-**4a** and (+)-**4b** were the same as those of the meso-compounds.

Preparation of (S,S)-(-)-2,16-Di-t-butyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1] heneicosa-1(21),17,19-triene (6a) (Scheme 2). A suspension of NaH (80 % in mineral oil, 0.14 g, 4.67 mmol) in dioxane (25 mL, dried over molecular sieves) was stirred at rt under Ar. To this suspension was added a solution of the (S,S)-(-)-**3** (0.190 g, 0.756 mmol) in dioxane (60 mL). The mixture was heated to 70 °C and stirred for 3 h, after which a solution of tetraethylene glycol ditosylate (0.45 g, 0.895 mmol) in dioxane (30 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at 70 °C for 6 days, after which the reaction was quenched by the addition of 40 mL of distilled H$_2$O. The mixture was concentrated under reduced pressure, and the residue was dissolved in an ether/water mixture. The organic layer was

removed, and the aqueous layer was extracted with ether (50 mL x 5). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 0.26 g of an oil. This oil was eluted from an alumina column with 100/1: $C_6H_5CH_3/C_2H_5OH$ to give 0.14 g of crude product. This material was eluted from a silica gel column with $C_6H_5CH_3$ and then with 100/1: $C_6H_5CH_3/C_2H_5OH$ to give 0.0501 g of (*S,S*)-(-)-**6a** (16 %) as an oily white solid; $[\alpha]^{25}_D$ -28.8 °(c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.58 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 2H), 4.21 (s, 2H), 3.75 - 3.40 (m, 16H), 0.92 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 164.2, 134.6, 122.0, 77.7, 71.0, 70.7, 70.6, 69.4, 29.7, 26.5; Anal. Calcd for $C_{23}H_{39}NO_5$: C, 67.45; H, 9.60. Found: C, 67.29; H, 9.36; EI-MS: 353 ($M^+ - C_4H_9$, 100 %), 409 (M^+, 6 %); FAB-MS: 432 ($M+Na^+$, 100 %).

Preparation of meso-2,16-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (5a) (Scheme 2). Meso-α,α'-dimethylpyridinedimethanol (meso-**2**) was treated with tetraethyleneglycol ditosylate in a similar manner as above for the synthesis of (*S,S*)-(-)-**6a**. After the reaction mixture was treated in the usual manner, the residual oil was separated and purified on an alumina column ($C_6H_5CH_3/C_2H_5OH$: 300/1) and then gel-permeation (Sephadex-LH20 with C_2H_5OH as the eluent). Macrocycle meso-**5a** was obtained in a 4.8 % yield as an oil; ^1H NMR δ ($CDCl_3$): 7.73 (t, *J*= 7.7 Hz, 1H), 7.36 (d, *J*= 7.7 Hz, 2H), 4.69 (q, *J*=6.6 Hz, 2H), 3.73 - 3.38 (m, 16H), 1.50 (d, *J*= 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 162.2, 137.2, 119.0, 79.5, 70.8, 70.6, 70.4, 68.1, 21.9; HRMS; Calcd for $C_{17}H_{27}NO_5$: 326.1967. Found: 326.1977.

Preparation of (*S,S*)-(-)-2,16-Dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1] heneicosa-1(21),17,19-triene (5a) and (*S,S,S,S*)-2,16,22,36-Tetramethyl-3,6,9,12,15,23,26, 29,32,35-decaoxa-41,42-diazatricyclo[36.3.1.1^{17,21}]dotetraconta-1(41),17,19,21,37,39-hexaene (5b) (Scheme 2). (*S,S*)-(-)-α,α'-Dimethylpyridinedimethanol was reacted and the products were purified as above for the preparation of (*S,S*)-(-)-**6a** to give (*S,S*)-(-)-**5a** and (*S,S,S,S*)-(-)-**5b** as oils in 1.5 % and 0.4 % yields, respectively. (*S,S*)-(-)-**5a** exhibited the following properties, $[\alpha]^{25}_D$ = - 2.2 ° (c = 1.0, $CHCl_3$); HRMS; Calcd for $C_{17}H_{27}NO_5$: 326.1967. Found: 326.1975. The

^{1}H and ^{13}C NMR spectra of (*S,S*)-(-)-**5a** were the same as those of meso-**5a**. (*S,S,S,S*)-**5b** exhibited the following properties, ^{1}H NMR δ (CDCl$_3$): 7.64 (t, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 4H), 4.69 (q, *J* = 6.5 Hz, 4H), 3.74 - 3.48 (m, 32H), 1.51 (d, *J* = 6.5 Hz, 12H); ^{13}C NMR (CDCl$_3$): δ 162.2, 136.7, 119.8, 78.8, 70.6, 70.5, 67.7, 22.0; FAB-MS: 326 (M$^+$/2+1 100 %), 348 (325+Na$^+$, 55 %), 364 (M$^+$/2+CH$_2$+Na$^+$ 11%), 378 (M$^+$/2+CH$_2$CH$_2$+Na$^+$, 3 .%), 386 (M$^+$/2+OCH$_2$CH$_2$O, 1.2 %), 503 (M$^+$ - O(CH$_2$CH$_2$O)$_3$, < 0.5 %), 547 (M$^+$ - O(CH$_2$CH$_2$O)$_2$, < 0.5 %), 675 (M$^+$+Na$^+$, 0.8 %). The optical rotation of (*S,S,S,S*)-**5b** could not be measured because there was not enough compound.

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Figure captions.

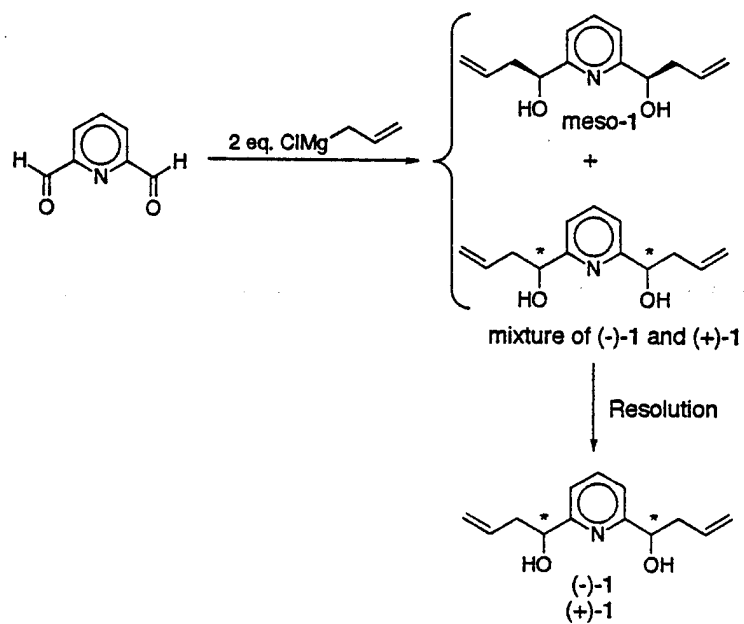Scheme 1. Preparation of meso, (-)- and (+)-α,α'-diallyl-2,6-pyridinedimethanol.

Scheme 2. Preparation of meso and chiral pyridino-18-crown-6 and dipyridino-36-crown-12 ligands.

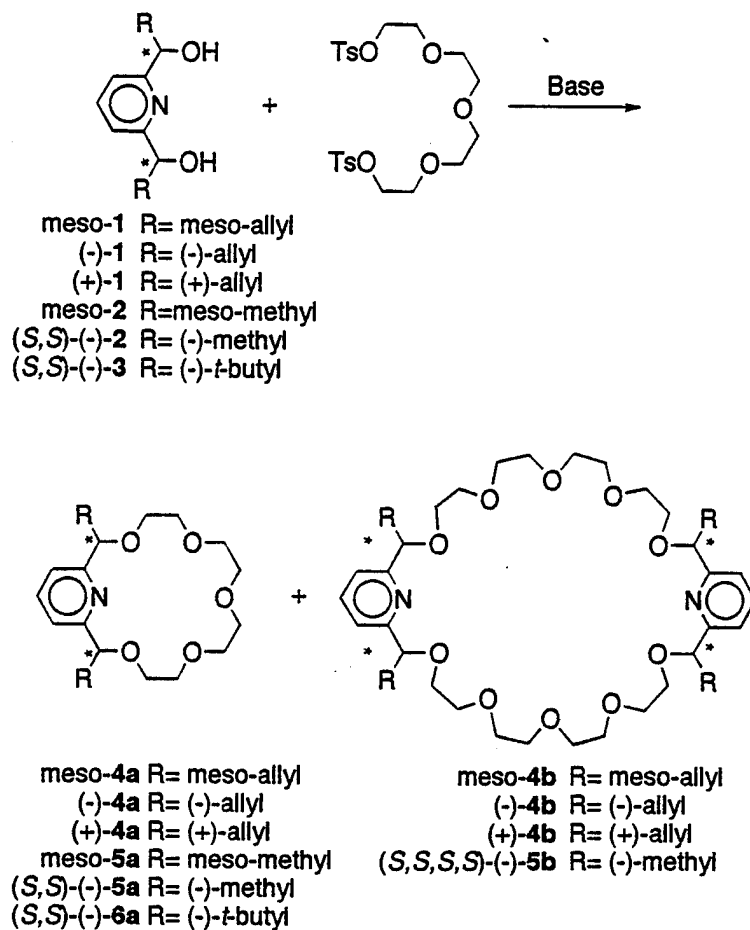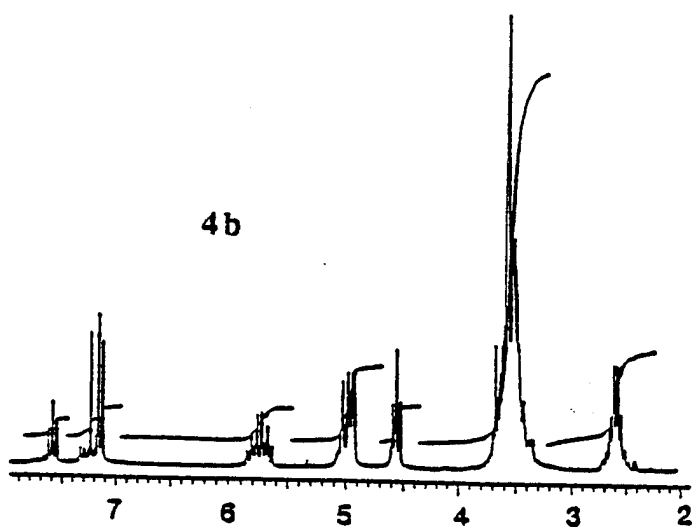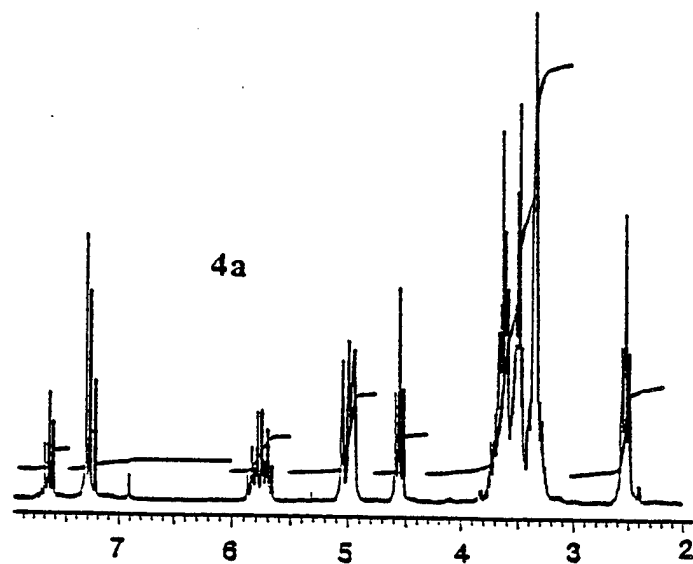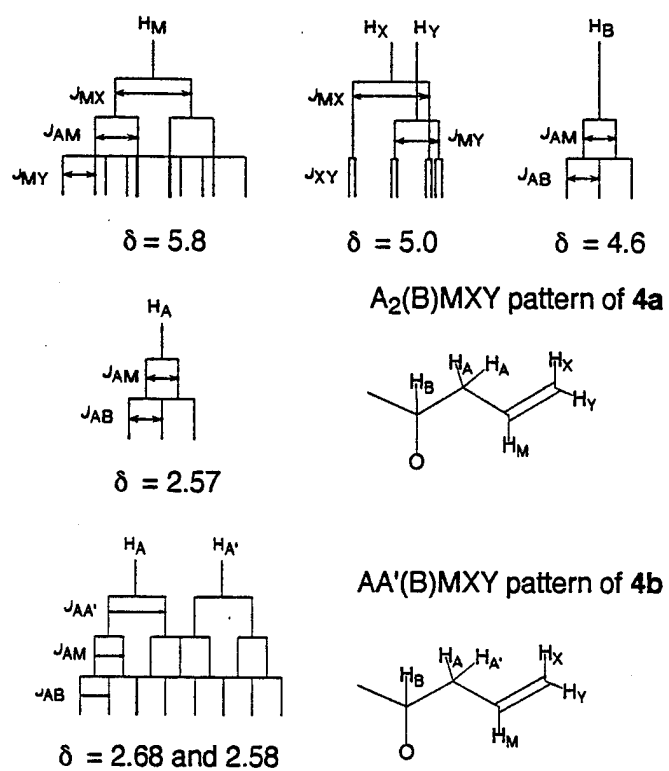Figure 1. ^{1}H NMR spectra of **4a** and **4b** in CDCl$_3$.

Figure 2. Splitting patterns of allyl moiety protons of **4a** and **4b**.

Figure 3. H$_A$ and H$_{A'}$ proton signals of **4a** and **4b**. **4a**: Before (a) and after (b) irradiation to H$_B$ protons. **4b**: Before (c) and after (d) irradiation to H$_B$ protons.

Figure 4. Postulated cleavage patterns of **4b**.

Scheme 1. Preparation of meso, (-)- and (+)-a,a'-diallyl-2,6-pyridinedimethanol.

meso-1 R= meso-allyl
(-)-1 R= (-)-allyl
(+)-1 R= (+)-allyl
meso-2 R=meso-methyl
(S,S)-(-)-2 R= (-)-methyl
(S,S)-(-)-3 R= (-)-t-butyl

meso-4a R= meso-allyl
(-)-4a R= (-)-allyl
(+)-4a R= (+)-allyl
meso-5a R= meso-methyl
(S,S)-(-)-5a R= (-)-methyl
(S,S)-(-)-6a R= (-)-t-butyl

meso-4b R= meso-allyl
(-)-4b R= (-)-allyl
(+)-4b R= (+)-allyl
(S,S,S,S)-(-)-5b R= (-)-methyl

Scheme 2. Preparation of meso and chiral pyridino-18-crown-6 and
dipyridino-36-crown-12 ligands.

Figure 1. ^{1}H NMR spectra of 4a and 4b in CDCl$_3$.

Figure 2. Splitting patterns of allyl moiety protons of **4a** and **4b**
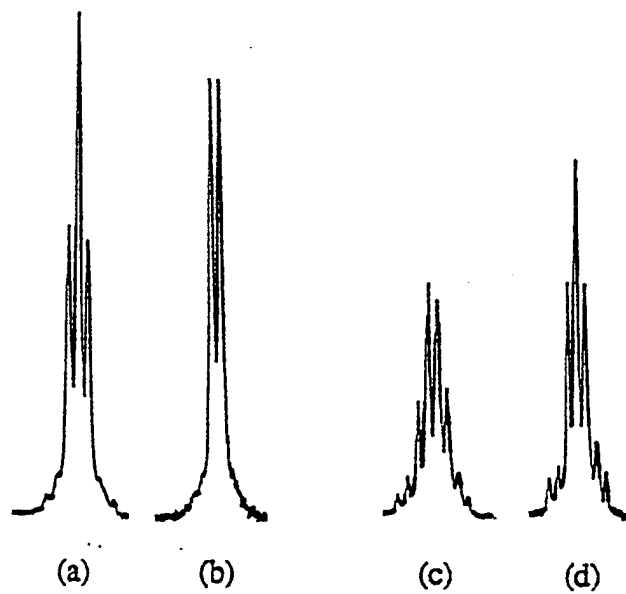
Figure 3. H_A and $H_{A'}$ proton signals of 4a and 4b.
4a: Before (a) and after (b) irradiation to H_B protons.
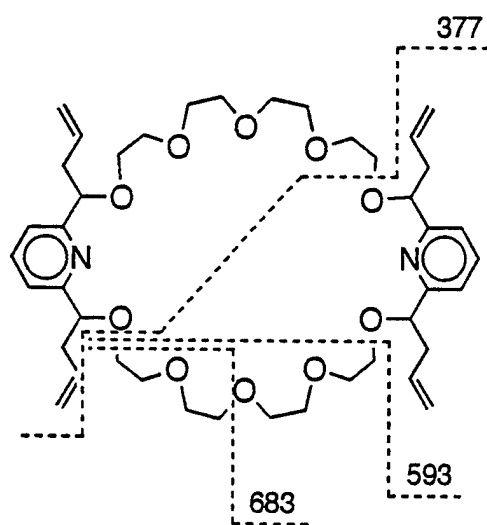4b: Before (c) and after (d) irradiation to H_B protons.

Figure 4. Postulated cleavage patterns of **4b**.